The Effect of Race/Ethnicity on the Outcome of Highly Active Antiretroviral Therapy for Human Immunodeficiency Virus Type 1–Infected Patients

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We performed a population-based cohort study to assess the impact of nonwhite origin on the outcome of highly active antiretroviral therapy (HAART) for a Danish cohort of human immunodeficiency virus (HIV)–infected patients. A total of 389 whites and 135 nonwhites started receiving HAART before 1 April 2001. After 1 year of treatment, 78% of nonwhites and 76% of whites achieved a virus load of <500 HIV RNA copies/mL. No major differences were found between the 2 groups with respect to achievement of a virus load of <500 copies/mL (relative risk [RR], 0.94; 95% confidence interval [CI], 0.74–1.18), risk of clinical progression (RR, 0.63; 95% CI, 0.32–1.24), or response measured by total CD4+ cell count. One year after fulfilling Danish recommendations for initiation of HAART, 91% of nonwhites and 93% of whites had started receiving HAART. Race and ethnic origin play no major role in the outcome associated with HAART if access to health care is free.

The introduction of HAART has improved the prognosis of HIV infection considerably. However, several cohort studies have indicated that the treatment response varies according to socioeconomic status, race/ethnicity, age, and history of injection drug use [1–4].

In most countries in North America and western Europe, including Denmark, there has been a shift in the HIV epidemic: increasing numbers of nonwhites and women are becoming infected, and more cases of infection are occurring as a result of heterosexual contact [5–8]. Most nonwhite HIV-infected patients in Denmark are first-generation immigrants from countries in which there is a high prevalence of HIV infection (in particular, sub-Saharan Africa); these individuals potentially have a very different social and cultural background from Danish natives.

A successful treatment outcome requires strict adherence to the prescribed regimen and, thus, the ability to cope with a substantial pill burden, frequent adverse events, and regular outpatient visits [9]. The use of the prescribed medicine may be influenced by several factors, such as language and communication barriers, different health beliefs, and stigmatization of HIV-infected individuals in the cultural community [10]. Several cohort studies have shown that nonwhites are less likely to be receiving HAART [11–13]. In Denmark, treatment for HIV infection and use of health care facilities are free, and the outcome of treatment is likely to be less influenced by the economic status of the patient.
per se. We examined whether race was associated with the initiation of and response to HAART among adult HIV-infected patients from a population-based cohort study in western Denmark.

**MATERIALS AND METHODS**

**Demographics of HIV infection and health care in Denmark.** As of January 2001, Denmark had a population of 5,350,000 individuals, 55.1% of which lived in western Denmark, which includes Funen and Jutland. Immigration to Denmark from less developed countries has increased during the past 10 years [14]. As of January 2001, there was a total of 308,674 immigrants (3.8% of the entire population) in Denmark. The total number of African immigrants was 28,190, or 0.5% of the entire population; the majority of these immigrants were black Africans from sub-Saharan Africa.

National surveillance data notified a total of 2888 people with newly diagnosed HIV infection from September 1990 through May 2000 [7]. Immigrants accounted for 28% of new cases of HIV infection, 64% of which originated in Africa. The prevalence of immigrants among individuals with new cases of HIV infection increased from 17% in 1990 to 37% in 1999.

In Denmark, treatment for HIV infection is restricted to specialized, public centers; 5 of these centers are localized in western Denmark. As previously mentioned, the use of health care facilities and antiretroviral treatment is free. Strategies used for patient care and treatment are similar throughout the country, with routine visits planned every 3 months for patients receiving antiretroviral therapy and every 3–6 months for patients with an earlier stage of the disease. The main criteria for initiation of antiretroviral therapy are a CD4⁺ cell count of $<300 \times 10^3$/L, a plasma HIV RNA load of $>100,000$ copies/mL, or the presence of HIV-related disease.

**Study population.** The HIV Cohort Study in western Denmark is a multicenter, population-based cohort study of all HIV-positive individuals in the region of western Denmark (which, as of January 2001, had an adult population of 2,342,919 individuals). Study methods and cohort characteristics at baseline have been described in detail elsewhere [8].

In brief, all HIV-positive patients seen at one of the centers in the region after 1 January 1995 are included in the study. Until April 2001, a total of 842 patients aged $>15$ years were enrolled. The study is ongoing, and both individuals in the region with newly diagnosed HIV infection and HIV-positive individuals who have moved from another country to the region are continuously enrolled. Diagnoses of AIDS were recorded using the 1993 clinical definition of AIDS from the US Centers for Disease Control and Prevention (Atlanta, GA) [15]. Use of the Danish Civil Registration (CPR) number, a unique number provided to every person in Denmark since 1968, enables the centers to avoid multiple registrations of single patients and to track whether patients who are lost to follow-up have died or have moved outside the region.

**The HIV cohort.** In the analysis of the proportion of patients lost to observation and the proportion initiating HAART, the study population consisted of adult patients (age, $>15$ years) who had HIV-1 infection diagnosed after December 1994 and who met $\geq 1$ of the criteria for the initiation of HAART (i.e., a CD4⁺ cell count of $<300 \times 10^3$/L, a plasma HIV RNA load of $>100,000$ copies/mL, or the presence of HIV-related disease) after 1 January 1997. Patients eligible for analysis of the response to HAART (virological, immunologic, and clinical) were adult patients (age, $>15$ years) in the cohort who were receiving HAART before 1 April 2001.

**Outcome measures.** To examine whether only a limited group had access to antiretroviral treatment, we estimated the proportion of patients who met $\geq 1$ of the 3 criteria for initiation of HAART but who were lost to observation and thus were not eligible to receive treatment. Being lost to observation was defined as emigrating from the region or having the last visit at one of the centers before 1 January 2000. We then estimated the proportion of patients who actually did start receiving HAART after meeting positive criteria for treatment. Throughout the study, HAART was defined as a treatment regimen that included a minimum of 3 antiretroviral drugs.

To evaluate the response to HAART, the outcomes of interest were the proportion of patients who achieved a plasma HIV RNA load of $<500$ copies/mL during follow-up, the proportion with a plasma HIV RNA load of $<500$ copies/mL together with the absolute CD4⁺ cell count after 60, 120, and 180 weeks of follow-up, and clinical progression (defined as a new AIDS-defining event or death due to any cause). In the calculations of HIV RNA loads and CD4⁺ cell counts during follow-up, the values were grouped according to 12-week intervals. Values measured during the period from 4 weeks before to 8 weeks after the specific date were included in the 12-week interval. If $>1$ value of the parameter was available for the period, the mean was calculated for the CD4⁺ cell count, and the mean of the log-transformed HIV RNA load was calculated for the virus load. If no CD4⁺ cell count or virus load was available for a 12-week interval, the missing parameter was replaced by the value from the previous period (i.e., the principle of "last value carried over"). A virus load was considered undetectable when there were $<500$ copies/mL, because this value represented the highest level of sensitivity for all the test systems used in the observation period. Missing virus loads were regarded as detectable ($>500$ copies/mL); however, when the virus load just before and after a missing virus load was undetectable, then the missing virus load was considered undetectable.
Data analysis. Baseline clinical and laboratory characteristics were compared between the 2 groups by use of χ², Mann-Whitney, and Fisher’s exact tests. To summarize the risk of being lost to observation over time, the risk of actually starting HAART, the risk of achieving an undetectable virus load, and the risk of clinical progression, we used Kaplan-Meier analysis to construct survival curves. In these time-to-event analyses, the Cox proportional-hazards regression model was used to compare the risk between whites and nonwhites, estimating the risk ratio (RR) and associated 95% CIs, which were adjusted for the following potential confounders: sex, age, history of injection drug use, year of HIV diagnosis, and previous AIDS-defining event. In the analysis of the risk of being lost to observation and the risk of starting HAART, the estimates were additionally adjusted for the CD4⁺ cell count and virus load at diagnosis. In the analysis of the risk of achieving an undetectable virus load and the risk of clinical progression, the estimates were additionally adjusted for the CD4⁺ cell count at the time of initiation of HAART, the virus load at the time of initiation of HAART, antiretroviral treatment–naïve status, year of initiation of HAART (up to or after 1998), and receipt of saquinavir hard-gel capsules as the initial protease-inhibitor component. Age, CD4⁺ cell count, and virus load were modeled as continuous variables. Selection of variables was done according to the change-in-estimate method, in which variables resulting in changes in the estimated exposure effect of ≥10% were entered in the final model [16]. The assumption of proportional hazards was assessed graphically by comparing observed versus predicted values of “survival” probabilities for each group.

In the prevalence analysis of patients who had an undetectable virus load at 60, 120, and 180 weeks after initiation of HAART, we used the logistic regression model to compare the prevalence in whites and nonwhites. ORs and associated 95% CIs, adjusted for potential confounders (see the above analysis of the risk of achieving an undetectable virus load), were estimated. Hosmer-Lemeshow goodness-of-fit tests were used to test the validity of the model [17].

The absolute CD4⁺ cell counts at weeks 60, 120, and 180 were compared between the 2 groups by use of a multivariate linear regression model, which also was adjusted for potential confounding variables (see the above analysis of the risk of achieving an undetectable virus load). Residual plots were produced to check the model assumptions. CD4⁺ cell counts were square root–transformed to restore a normal distribution. Data analysis was performed using SPSS statistical software, version 10.0 (Norusis; SPSS), and SAS statistical software, version 6.12 (SAS Institute).

RESULTS

Lost to Observation and Initiation of HAART

Of the 524 patients who started receiving HAART, 394 had HIV infection diagnosed after December 1994. Of these patients, 270 (165 whites and 105 nonwhites) met ≥1 of the criteria for the initiation of HAART after 31 December 1996. Seventy-nine (75.2%) of the nonwhites were black Africans from sub-Saharan Africa.

The probability of being lost to observation after fulfilling the criteria for initiation of HAART was estimated for whites and for nonwhites. After 12 months, 7 whites and 9 nonwhites were lost to observation (data not shown). Cox proportional-hazards analyses showed a nonsignificant increased risk among nonwhites, with an adjusted RR of 2.12 (95% CI, 0.77–5.81) (unadjusted RR, 1.81; 95% CI, 0.73–4.44). Only 7 patients (6 whites and 1 nonwhite) died without starting HAART after fulfilling positive treatment criteria.

The cumulative probability of starting HAART after meeting the treatment criteria is shown in the Kaplan-Meier survival curve (figure 1). Although both groups were treated to the same extent during the follow-up period, the nonwhites started receiving treatment later than did the whites. Hence, after 6 and 12 months of follow-up, an estimated 74.1% and 91.0% of nonwhites, respectively, had started treatment, compared with 83.7% and 93.0% of whites, respectively. Cox regression analysis showed an adjusted RR of 0.59 (95% CI, 0.44–0.78) (unadjusted RR, 0.70; 95% CI, 0.53–0.93), confirming the delay in initiation of HAART among nonwhites.

Response to HAART

Of the 842 patients in the cohort, 524 adults (age, >15 years) had started receiving HAART before 1 April 2001. The demographic and baseline characteristics of the patients at the time of initiation of HAART are presented in table 1. Of the 135 nonwhites, 98 were black Africans from sub-Saharan Africa. Only 2 nonwhites were of Danish origin; the remaining nonwhites were first-generation immigrants. Seven nonwhites had HIV infection diagnosed before arrival in Denmark; for the rest, the median duration of stay in Denmark before diagnosis was 1.57 years.

The 2 groups differed in several ways: the nonwhites were less dominated by males (25.9% vs. 83.0%), were more likely to report heterosexual contact as the primary mode of transmission (85.9% vs. 41.6%), were younger (median age, 33.4 years vs. 40.1 years), and had a lower CD4⁺ cell count at the time of initiation of HAART (168 × 10⁶ cells/L vs. 203 × 10⁶ cells/L), had a slightly higher virus load (4.81 log HIV RNA copies/mL vs. 4.76 log HIV RNA copies/mL), and were more likely to be antiretroviral naive at initiation of HAART (61.5% vs. 49.9%). Nonwhites had a shorter follow-up (median, 121
Virological response. The cumulative probability of achieving a plasma virus load of <500 HIV RNA copies/mL after initiation of HAART is shown in figure 2. The Kaplan-Meier plots show a steep decrease in the proportion of patients with detectable virus loads for both groups. Overall, the proportion that achieved an undetectable virus load at 12 months was 76.5% (95% CI, 72.7–80.3); an estimated 76% of whites and 78.1% of nonwhites. The crude risk estimates indicated an increased risk among nonwhites with an RR of 1.27 (95% CI, 1.02–1.58). However, after adjustment for potential confounders, the RR decreased to 0.94 (95% CI, 0.74–1.18), indicating no major differences between the 2 groups in achieving an undetectable virus load after initiation of HAART.

Figure 3A shows the percentage of patients with an undetectable virus load at 12-week intervals up to 180 weeks after initiation of HAART. Slightly fewer nonwhites had undetectable virus loads after week 24. Application of logistic regression analysis revealed no major difference between the groups, with adjusted ORs of 0.60 (95% CI, 0.35–1.04), 0.55 (95% CI, 0.30–1.00), and 1.63 (95% CI, 0.66–4.07) at 60, 120, and 180 weeks, respectively.

Immunologic response. Figure 3B shows the 12-weekly median absolute CD4+ cell counts for whites and nonwhites after the start of HAART. As mentioned in the analysis of baseline characteristics, the nonwhites had a lower median baseline CD4+ cell count, and the slightly lower values persisted during the follow-up period. However, the increase in the median CD4+ cell count after initiation of HAART was similar in both groups. At 60 weeks, the median CD4+ cell count had increased by $114 \times 10^3$ cells/L and $112 \times 10^3$ cells/L for whites and nonwhites, respectively. The median CD4+ cell counts were compared for each of the weeks 60, 120, and 180 by use of a multiple linear-regression model. The regression coefficients (for the square root–transformed values) were 1.76 (P = .004), 1.36 (P = .11), and 0.80 (P = .52) for weeks 60, 120, and 180, respectively.

Clinical response. Overall, 74 patients had clinical progression during follow-up after initiation of HAART: 35 had a new AIDS-defining event, and 39 died. Fifty-eight white patients (15.0%) and 16 nonwhite patients (11.9%) had clinical progression. Figure 4 shows the Kaplan-Meier curves for time to clinical progression for whites and nonwhites. When adjusting for potential confounders, there was a nonsignificant decreased risk of progression among the nonwhites, with an RR of 0.63 (95%, CI 0.32–1.24) (unadjusted RR, 1.15; 95% CI, 0.66–2.01).

DISCUSSION

We evaluated the response to, and initiation of, HAART among HIV-infected patients from a population-based cohort in western Denmark, focusing on the influence of racial/ethnic origin.

Figure 1. Time to initiation of HAART after criteria for treatment were met (i.e., a CD4+ cell count of $<300 \times 10^3$ cells/L, a plasma HIV RNA load of $>100,000$ copies/mL, or the presence of HIV-related disease).
We found no major differences between whites and nonwhites with respect to the virological, immunologic, or clinical responses to HAART. However, nonwhites started receiving treatment after a longer period of latency.

The main strength of our study is the uniformly organized health care system with primary catchment areas, which allowed a population-based design and the ability to follow patients over time. The main limitation of the study is the relatively small size of the cohort compared with other large observational cohorts of HIV-infected patients. However, because HIV treatment in the region is restricted to the hospitals, and because all of the centers treating HIV-infected patients in the region participated in the study, the cohort gives very detailed data on the HIV epidemic in a region of 2.3 million people. The validity of the data is furthermore secured by the use of CPR numbers for all individuals in Denmark, which allows us to

**Table 1. Demographic and baseline data for the study population at the time of initiation of HAART.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whites (n = 389)</th>
<th>Nonwhites (n = 135)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of total patients</td>
<td>74 (19.0)</td>
<td>26 (19.0)</td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>323 (83.0)</td>
<td>35 (25.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, median years</td>
<td>40.1</td>
<td>33.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Transmission category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men who have sex with men a</td>
<td>177 (45.5)</td>
<td>8 (5.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>162 (41.6)</td>
<td>116 (85.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>28 (7.2)</td>
<td>4 (3.0)</td>
<td>.08</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>22 (5.7)</td>
<td>7 (5.2)</td>
<td>.84</td>
</tr>
<tr>
<td>Danish origin</td>
<td>371 (95.4)</td>
<td>2 (1.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CD4+ cell count, median × 10⁹ cells/L</td>
<td>203 (52.3)</td>
<td>168 (50.0)</td>
<td>.23</td>
</tr>
<tr>
<td>HIV RNA load, median log₁₀ copies/mL</td>
<td>4.76</td>
<td>4.81</td>
<td>.89</td>
</tr>
<tr>
<td>Previous AIDS-associated event</td>
<td>90 (23.1)</td>
<td>23 (17.0)</td>
<td>.14</td>
</tr>
<tr>
<td>Antiretroviral treatment naive</td>
<td>194 (49.9)</td>
<td>83 (61.5)</td>
<td>.02</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless otherwise indicated.

*a Homosexual or bisexual contact.

**Figure 2.** Time from initiation of HAART to first measurement of a virus load of <500 HIV RNA copies/mL.
investigate whether patients lost to observation have died, emigrated, or are still living in the region. Because the study is observational, the results might be influenced by several types of bias [18]. However, the risk of recruitment bias is extensively reduced, because all known HIV-infected patients seen at the hospitals and outpatient departments in the area were included. Furthermore, to eliminate the extent of survival bias, only patients with HIV diagnosed after December 1994 were included in the analysis of the initiation of HAART.

Only a few studies have focused mainly on the association of racial/ethnic background with the response to HAART. In a cohort study from the United States, Anastos et al. [1] found that being nonwhite was a predictor for suboptimal response to antiretroviral treatment. However, there are several very important differences between health care in the United States and that in Denmark. Most importantly, access to health care and antiretroviral treatment is free in Denmark—that is, the outcome is not affected by the financial status of the patient per se. When cohort studies performed in countries such as the United States find that racial/ethnic background is a predictor for suboptimal outcome of antiretroviral treatment, nonwhite background will be closely linked to relatively poorer access to health care. The relationship between race, social class, and health has been documented in several studies [19, 20]. Consequently, fewer patients might be offered treatment, differential adherence might be more pronounced, and there will be a longer period of latency before HIV is diagnosed and before treatment is started. The latter consequence might be one of the explanations why relatively more AIDS cases are found among nonwhites in analysis of surveillance data on HIV [21].

Another factor of importance may be that the large majority of HIV-infected nonwhites in Denmark are first-generation immigrants, who bring a potentially very different social and cultural background from their country of origin. This is reflected by the short median length of time that nonwhites spent in Denmark (1.57 years) before HIV infection was diagnosed. The

Figure 3. Virological and immunologic responses after initiation of HAART. A, Proportion of patients with a virus load of <500 HIV RNA copies/mL after initiation of HAART. B, Absolute CD4+ cell count after initiation of HAART.
resulting difference in perceptions of medicine and its use does not seem to influence the outcome of treatment in western Denmark. Adherence to the prescribed treatment regimen was not directly evaluated in our study; however, our results and, in particular, the similarity in the proportions of individuals who had an undetectable virus load during follow-up, do not indicate major differences in adherence to therapy. However, the nonwhites, even black Africans, constitute very heterogeneous groups from several nations with very different cultures.

Several studies have shown an association between the complexity of the prescribed regimen and the degree of adherence [22]. Newer and simpler treatment regimens that are as potent as the more complex regimens have been introduced [23, 24]. With this in mind, there might be a tendency in clinical practice to offer simpler regimens to patients with predicted adherence difficulties—for example, nonwhites. Furthermore, because nonwhites have a shorter median follow-up, with more patients being treatment naive, they might benefit from newer and more-potent regimens and might develop fewer resistance mutations.

From our study, it appears that it is not a small and highly selected proportion of patients among nonwhites who start treatment. The number of patients who were lost to observation or who died after meeting the criteria for HAART and before the start of treatment was relatively small and was no different from that noted for whites. However, nonwhites had a longer delay before the start of treatment after fulfilling the criteria for HAART, which explains, in part, the lower CD4+ cell count at the time of initiation of treatment. The longer delay could be the result of patient-related factors or of factors related to the health care system. As previously mentioned, a growing number of patients in western Europe with new diagnoses are nonwhites; they constituted 40% of patients with newly diagnosed HIV infection in western Denmark during 2000. Hence, a continuously increasing number of patients living with HIV will be of nonwhite origin, a fact that the health care system will have to accept and deal with.

Our study would argue against a role for viral subtypes in differential treatment responses, given that the majority of Danish patients suspected of being infected abroad (especially in Africa) would harbor non-B viral subtypes [25]. Similarly, Frazier et al. [26] found no association between treatment response and HIV-1 clade or baseline polymorphisms in reverse transcriptase and protease. Nor do our findings suggest that host genetic factors shown to be present in different frequencies between the races play any role in treatment response, as has been proposed with the CCR5 gene 32-bp deletion or the C3435T polymorphism of the human MDR1 gene [27–33].

In conclusion, when access to health care is free, race/ethnic background does not play a major role in the virological, immunologic, or clinical response to HAART among HIV-infected patients. However, initiation of HAART was delayed for nonwhites, a fact that could not be explained by differences in the proportion lost to observation. An increasing number of patients with HIV infection in Denmark will be of nonwhite origin, and the health care system will have to implement treatment programs for this group to avoid delay in the receipt of treatment.
References


